Predictors of Early Acute Lung Injury at a Combat Support Hospital: A Prospective Observational Study

Jason W. Edens, MD, Kevin K. Chung, MD, Jeremy C. Pamplin, MD, Patrick F. Allan, MD, John A. Jones, BS, Booker T. King, MD, Leopoldo C. Cancio, MD, Evan M. Renz, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, John B. Holcomb, MD, and Lorne H. Blackbourne, MD

Background: Acute lung injury (ALI) is a syndrome consisting of noncardiogenic acute hypoxemic respiratory failure with the presence of bilateral pulmonary infiltrates and occurs in up to 33% of critically ill trauma patients. Retrospective and observational studies have suggested that a blood component resuscitation strategy using equal ratios of packed red blood cells (PRBCs) and fresh frozen plasma (FFP) may have a survival benefit in combat casualties. The purpose of this study was to determine whether this strategy is associated with an increased incidence of ALI.

Methods: We performed a prospective observational study of all injured patients admitted to an intensive care unit (ICU) at a combat support hospital who required >5 units of blood transfusion within the first 24 hours of admission. Baseline demographic data along with Injury Severity Score (ISS), pulmonary injury, presence of long bone fracture, blood products transfused, mechanical ventilation data, and arterial blood gas analysis were collected. The primary endpoint of the study was the development of ALI at 48 hours after injury. Those who did not survive to ICU admission were excluded from analysis. Follow-up (including mortality) longer than 48 hours was unavailable secondary to rapid transfer out of our facility. A multivariate logistic regression was performed to determine the independent effects of variables on the incidence of early ALI.

Results: During a 12-month period (from January 2008 to December 2008), 87 subjects were studied; of these, 66 patients met inclusion criteria, and 22 patients developed ALI at 48 hours (33%). Overall, the ratio of FFP to PRBC was 1:1.1. Those who developed ALI had a higher ISS (32 ± 15 vs. 26 ± 11; $p = 0.04$) and received more units of FFP (22 ± 15 vs. 12 ± 7; $p < 0.001$), PRBCs (22 ± 16 vs. 13 ± 7; $p = 0.008$), and platelets (5 ± 11 vs. 1 ± 2; $p = 0.004$) compared with those who did not develop ALI. Multivariate logistic regression analysis revealed that presence of pulmonary injury (odds ratio, 5.4; 95% confidence interval, 1.3–21.9) and volume of FFP transfused (odds ratio, 1.2; 95% confidence interval, 1.1–1.3) had independent effects on ALI at 48 hours.

Conclusion: On the basis of this small, prospective, descriptive study of severely injured patients admitted to the ICU, we determined that the presence of pulmonary injury had the greatest impact on the incidence of early ALI. There was also an independent relationship between the amount of FFP transfused and the incidence of early ALI. Further studies are required to determine the effects of the development of early ALI from FFP transfusion on short- and long-term survival.

Key Words: Fresh frozen plasma, Acute lung injury, Combat support hospital, Transfusion-related acute lung injury, Blood transfusion.

(*J Trauma.* 2010;69: S81–S86)

Damage control resuscitation has dramatically altered the initial care of severely injured soldiers at combat support hospitals (CSHs) who require massive transfusion.[1] This concept uses two strategies: resuscitation is limited to maintain systolic blood pressure at ~90 mm Hg, and intravascular volume is restored primarily with blood component therapy. Both military and civilian observational and retrospective studies have suggested a potential survival benefit for trauma patients resuscitated with ratios of fresh frozen plasma (FFP) to packed red blood cells (PRBCs) approaching 1:1.[2–5] These recent findings have altered transfusion practices throughout combat casualty care, and current military guidelines recommend administering FFP and PRBC in 1:1 ratios to injured patients requiring massive transfusion.

Although blood product transfusions may be necessary in severely injured patients, they are not free from risks. In addition to the traditional transfusion complications such as fever, infection, allergic and anaphylactic reactions, hemolysis, and fluid overload,[6,7] PRBC, FFP, and fresh whole blood (FWB) are associated with immunosuppression,[8] transfusion-related acute lung injury (TRALI), and worse outcomes following trauma.[9] Of these, TRALI represents a high rate of morbidity and mortality in those patients affected, and according to reports from the Food and Drug Administration (FDA), TRALI has become the leading cause of transfusion-related fatalities, with most fatal cases associated with transfusion of FFP.[10,11]

Because the shift in transfusion practices patterns toward a FFP:PRBC ratio closer to 1:1, there have been no published reports on its impact on acute lung injury (ALI). We wished to evaluate the impact of this transfusion practice on the incidence of early ALI with the hypothesis that

Submitted for publication March 1, 2010.
Accepted for publication April 22, 2010.

From the United States Army Institute of Surgical Research (J.W.E., K.K.C., J.A.J., B.T.K., L.C.C., E.M.R., S.E.W., C.E.W., L.H.B.), Fort Sam Houston, Texas; Madigan Army Medical Center (J.C.P.), Fort Lewis, Washington; Landstuhl Regional Medical Center (P.F.A.), Landstuhl, Germany; University of Texas Health Science Center at San Antonio (S.E.W.), Texas; and University of Texas Health Science Center at Houston (J.B.H.), Texas.
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.
Address for reprints: Kevin Chung, MD, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, TX 78234; email: Kevin.chung@amedd.army.mil.

DOI: 10.1097/TA.0b013e3181e44a32

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUL 2010	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Predictors of early acute lung injury at a combat support hospital: a prospective observation study	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Edens J. W., Chung K. K., Pamplin J. C., Allan P. F., Jones J. A., King B. T., Cancio L. C., Renz E. M., Wolf S. E., Wade C. E., Holcomb J. B., Blackbourne L. H.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**6**	

patients who receive a higher ratio of FFP:PRBC will develop a higher incidence of ALI.

PATIENTS AND METHODS

The Institutional Review Board approved this prospective observational study of all traumatically injured patients admitted to an intensive care unit (ICU) at a combat support hospital (CSH) who required >5 units of blood transfusion within the first 24 hours of admission. All US military, US civilian, and nondetainee foreign national patients were eligible for enrollment into the study, but patients designated as "suspected insurgents" or detainees were excluded. The definition of ALI used for this study, adopted from the American-European Consensus Conference,[12] included acute onset of hypoxemia with a partial pressure of arterial oxygen to fraction of inspired oxygen (P/F) ratio of less than 300 along with bilateral infiltrates on chest radiograph without evidence of cardiogenic pulmonary edema. All chest radiographs were examined, and all patients with ALI had the presence of bilateral infiltrates. Patients were followed for 48 hours or until evacuation from the CSH.

Pertinent demographic data including age, gender, nationality, ideal body weight, and mechanism of injury were collected prospectively on all patients. For ideal body weight, we used the predicted body weight based on the patient's height.[13] Other variables collected included Injury Severity Score (ISS), the presence of pulmonary injury or long bone fracture, blood transfusion data (including PRBC, FFP, platelets, cryoprecipitate, fresh whole blood (FWB), and factor VII), volume of crystalloid and colloid infusions, arterial blood gas analysis, mechanical ventilation data (including ventilator mode, tidal volume, and P/F ratio), and death by any cause. Pulmonary injury was defined as any blunt or penetrating injury to the thorax that resulted in a contusion, hemothorax, or pneumothorax diagnosed clinically or with chest radiographs. In instances of FWB use, we used the method of Borgman et al.[2] for inclusion of units of FWB into both the PRBC and FFP transfusion totals. Blood transfusion totals are the number of units received in the first 24 hours after injury. Mechanical ventilation data were recorded at time of admission, as well as 12, 24, and 48 hours after injury or until evacuation. The primary endpoint was development of early ALI (within 48 hours of injury). Those patients who did not survive to admission to the ICU were not included in analysis. Follow-up, including mortality, longer than 48 hours was unavailable secondary to rapid transfer out of the CSH.

Statistical analysis was performed using SAS version 9.1. Categorical data were analyzed with χ^2 or Wilcoxon two-sample tests when appropriate. Continuous data were analyzed using two-tailed Student's t test. Statistical significance was set at $p < 0.05$. Multivariate logistic regression was performed with ALI as the dependent variable to identify independent factors associated with the development of early ALI. Values are reported as mean ± SD, as odds ratios (ORs) ± 95% confidence intervals (CIs), or as percentages as applicable.

RESULTS

During a 12-month study period (from January to December 2008), 87 trauma patients admitted to the ICU at the CSH received >5 units of PRBC or equivalent during their initial resuscitation. There were six deaths within 12 hours of admission, and these patients were excluded from the study. Additionally, there were 15 patients who were either transferred from the CSH within the first 24 hours of admission or who had incomplete data, and they were also excluded from the study. The remaining 66 patients met inclusion criteria for the study, and 22 of these patients (33%) developed ALI within 48 hours. Eleven patients met the criteria of acute respiratory distress syndrome (ARDS) with P/F ratios <200. There was one death in the ALI group, whereas no patients from the non-ALI group died.

Demographic data demonstrated that patients were predominantly male (91%) with an average age of 28 years ± 8 years. There were 19 US military and civilian patients (29%) and 47 foreign national patients (71%) in the study group. Patients were severely injured, and the average ISS of all patients was 28.0 ± 12.8. Mechanisms of injury included gunshot wounds (n = 27, 41%) and explosions (n = 39, 59%). None of the patients in this study were the victims of blunt injury alone. Transfusion data of all patients demonstrated a mean of 16.2 units ± 11.6 units of PRBC and 15.0 units ± 10.9 units of FFP given during the initial 24 hours of resuscitation.

Table 1 compares patients with and without ALI. Patients who developed ALI were more severely injured with a significantly higher ISS and required significantly more blood products, including PRBC, FFP, and platelets, during their initial 24-hour resuscitation. Patients who developed ALI also received more colloid than those who did not develop ALI. Gunshot wounds were the cause of injury in 32% (n = 7) of patients who developed ALI and in 45% (n = 20) of those who did not develop ALI, whereas explosion injuries occurred in 68% (n = 15) of those who developed ALI and in 55% (n = 24) of those without ALI. There was no difference in the mechanism of injury on the development of ALI.

Multivariate logistic regression was performed to identify independent factors associated with the development of

TABLE 1. Comparison of Patients With and Without ALI

Variable	ALI (n = 22)	Non-ALI (n = 44)	p
Age (yr)	28.3 ± 7.5	28.2 ± 8.6	0.812
ISS	32.2 ± 14.6	25.8 ± 11.4	0.044
Pulmonary injury	11 (50%)	14 (32%)	0.151
Long bone fracture	7 (32%)	17 (39%)	0.587
PRBC (units)	22.3 ± 16.2	13.2 ± 6.9	0.008
FFP (units)	21.6 ± 14.6	11.7 ± 6.6	<0.001
FFP:PRBC (ratio)	1.0 ± 0.3	0.9 ± 0.3	0.059
Platelets (6 packs)	4.7 ± 11.2	1.1 ± 1.5	0.004
Crystalloid (L)	6.4 ± 3.1	5.1 ± 2.3	0.089
Colloid (L)	0.5 ± 0.6	0.3 ± 0.5	0.036
Initial tidal volume (mL/kg)	7.8 ± 1.1	7.4 ± 1.0	0.156

TABLE 2. Logistic Regression for Predictors of ALI at 48 h

Variable	Adjusted OR (95% CI)	*p*
FFP (units)	1.2 (1.08–1.33)	<0.01
Pulmonary injury	5.36 (1.30–21.93)	0.02
Initial tidal volume (mL/kg)	1.94 (1.02–3.70)	0.04
ISS	1.07 (1.00–1.15)	0.05
Injury mechanism	1.79 (0.61–5.24)	0.29
PRBC (units)	1.09 (0.74–1.58)	0.67
Platelets (6 packs)	0.96 (0.71–1.30)	0.81
Crystalloid (L)	1.24 (0.86–1.78)	0.25
Colloid (L)	3.19 (0.72–14.21)	0.13

FFP, the presence of a pulmonary injury, and initial tidal volume all had independent effects on ALI at 48 h.

early ALI (Table 2). The presence of pulmonary injury had the greatest impact on the development of early ALI, with an adjusted OR of 5.4 (95% CI, 1.3–21.9). Other factors that affected the development of early ALI included the initial tidal volume and volume of FFP transfused.

DISCUSSION

The concept of damage control resuscitation has dramatically altered transfusion practices throughout combat casualty care.[1] Changes in military combat casualty clinical practice followed the suggestion that increased ratios of FFP:PRBC approaching 1:1 given to severely injured patients requiring massive transfusion were associated with improved mortality rates.[2] Although this benefit in mortality has been observed in several observational and retrospective studies, there are inherent risks to transfusion of FFP. In particular to this study, we wished to see what impact these new transfusion protocols had on the incidence of early ALI, defined as ALI within 48 hours of injury. Additionally, we wished to determine whether other factors existed that could possibly predict the development of ALI in severely injured combat casualties. The observational findings in our study suggest that transfusion strategies using early FFP may be associated with a higher incidence of ALI. The clinical implications of this finding in relation to patient outcomes are unknown. Further larger studies are needed to fully address the role of FFP to ALI and outcome, and prospective, randomized controlled trials are needed to answer the question of whether 1:1 transfusion strategies result in improved outcomes versus more conservative component strategies.

ALI occurs in ~12% to 33% of critically injured patients[14–17] and up to 30% of patients with severe traumatic brain injury.[18] Severe trauma has been recognized as a precipitating cause of ALI and its progression into ARDS.[12,15,19,20] Hoyt et al. found that an ISS >16 was a significant risk factor for ARDS,[19] whereas Hudson et al. found that those with ISS >20 had a 1.5 times greater risk for ALI/ARDS.[20] More recently, Miller et al. demonstrated through univariate analysis that ISS >25 was associated with the development of ARDS (OR, 5.1; 95% CI, 3.8–6.8; $p < 0.0001$).[21] In line with these previous studies, there was a 33% incidence of ALI in our patient population. Additionally, the patients who developed ALI were more significantly injured than those patients who did not develop ALI (ISS, 32.2 ± 14.6 vs. 25.8 ± 11.4). ALI represents a devastating complication of traumatic injury that adds morbidity and mortality to these patients. A prospective cohort study of severely injured trauma patients who were admitted to the ICU showed that the development of ALI increased the duration of ICU stay and hospital cost, independent of trauma severity.[14] An additional study found that ALI contributed independently to hospital mortality, beyond baseline severity of illness, in critically ill trauma patients without isolated head injury.[17]

Although several factors may contribute to the development of ALI, pulmonary injuries including pulmonary contusion have been implicated in leading to ALI/ARDS in trauma patients.[22] Pulmonary contusions cause direct disruption of both alveolar and capillary membranes, promoting local and systemic inflammation largely due to the release of arachidonic acid metabolites.[23] These processes lead to varying degrees of pulmonary dysfunction and may progress to ALI or ARDS. In an experimental animal model in which pulmonary contusion was induced in swine after modest hemorrhagic shock, Batchinsky et al. showed that the cause of hypoxia in the early hours after contusion is the development of a true shunt with transient ventilation-perfusion mismatch and that aggressive resuscitation in the early post-contusion period may increase this shunt and contribute to the development of ALI/ARDS.[24] Although limiting the amount of resuscitation may not be feasible, pulmonary contusions themselves can contribute to the development of ALI/ARDS. An early study showed that 38% of patients with pulmonary contusion developed ARDS.[25] Miller et al. demonstrated that increasing contusion severity had a significantly higher association with the development of ARDS in patients with chest trauma.[26] Gong et al. showed through multivariate analysis that direct pulmonary injury was significantly associated with the development of ARDS (OR, 3.78; 95% CI, 2.45–5.81; $p < 0.001$).[27] In our study, pulmonary injury had the greatest impact on the incidence of early ALI (OR, 5.36; 95% CI, 1.30–21.93; $p = 0.02$) and was present in 50% of patients who developed ALI.

Blood transfusions have long been implicated in the development of ALI, leading to the clinical entity known as TRALI. First defined by Popovsky et al. in 1983,[28] TRALI is noncardiogenic pulmonary edema temporally related to the transfusion of blood products. This temporal relationship was further defined by the National Heart, Lung, and Blood Institute Working Group on TRALI, stating the diagnosis of TRALI is made if new ALI develops during or within 6 hours after a completed infusion of one or more plasma-containing or plasma-derived blood products.[29] More recently, Marik and Corwin identified a delayed TRALI syndrome that occurs in up to 25% of critically ill patients receiving a blood transfusion, develops 6 hours to 72 hours after the transfusion, and is associated with a mortality of up to 40%.[30] Two theories have been proposed to explain the pathophysiology of TRALI. The first hypothesis suggests an antibody-mediated reaction as leukocyte antibodies in donors

activate recipient neutrophils in pulmonary capillaries to cause pulmonary damage and capillary leak.[29] The second hypothesis represents the two-event model in which ALI/ARDS occurs as the result of at least two clinical insults.[31] The first is related to a clinical insult to the patient, such as recent surgery, trauma, or sepsis, which leads to pulmonary endothelial activation with sequestration of neutrophils. The second insult results from infusion of biologically active mediators, such as lipids or cytokines that can be found in plasma-derived blood products, which activate these adherent neutrophils and lead to endothelial damage, capillary leak, and ALI.

Several authors have shown the relationship between the transfusion of PRBCs and the development of ALI/ARDS. In a retrospective review of 4,397 blunt trauma patients admitted to the ICU, Miller et al.[22] demonstrated that transfusion >10 units PRBC in the first 24 hours after injury was associated with the development of ARDS (OR, 5.3; 95% CI, 3.4–8.0; $p < 0.0001$).[21] Another retrospective review of 5,260 blunt trauma patients who were less severely injured (ISS <25) by Croce et al. demonstrated a higher risk of ARDS in those patients who had received any transfusion (OR, 3.42; 95% CI, 4.02–34.12; $p = 0.0001$).[32] The amount of PRBC transfused and its association with the development of ALI/ARDS was the subject of a prospective cohort study by Silverboard et al.[33] In 102 consecutive patients with severe trauma, the authors found that patients who developed ARDS received significantly more blood products during their initial resuscitation. Patients receiving >10 units of PRBC had a 57% incidence rate compared with a 21% incidence rate in patients receiving 0 units to 4 units of PRBC ($p = 0.007$). Multivariate logistic regression showed an association between the number of units of transfusion and the development of ARDS between patients receiving 0 units to 4 units and those receiving >10 units (OR, 14.4; 95% CI, 3.2–78.7; $p = 0.002$). The authors also demonstrated an ~4% increased risk of ARDS for each additional unit of transfused blood. In accordance with these studies, our results showed that patients who developed ALI received significantly more units of PRBC when compared with those who did not develop ALI (22.3 ± 16.2 vs. 13.2 ± 6.9; $p = 0.008$). However, logistic regression did not demonstrate that PRBC transfusion was independently associated with the development of ALI.

Although several studies have shown that early FFP transfusion in severely injured trauma patients has mortality benefits,[2–5] many studies have shown a link between the transfusion of FFP and the development of ALI. Sperry et al.[35] studied bluntly injured trauma patients and showed that FFP:PRBC ratios ≥1:1.5 in patients requiring ≥8 units of blood transfusion were associated with a significantly lower risk of mortality (52% lower risk; hazard ratio [HR], 0.48; 95% CI, 0.3–0.8; $p = 0.002$), but a twofold higher risk of acute respiratory distress syndrome (HR, 1.93; 95% CI, 1.23–3.02; $p = 0.004$).[34] Further work in this same set of bluntly injured trauma patients showed that in patients surviving their initial injury, FFP had an overall protective effect and was not only associated with an independent 2.9% reduction in the risk of mortality for every unit transfused (HR 0.971; 95% CI, 0.945–0.997; $p = 0.027$) but was also independently associated with a 2.5% higher risk of ARDS (HR, 1.025; 95% CI, 1.001–1.049; $p = 0.038$) per unit transfused, with 3 units to 6 units of FFP having a 66.5% higher risk of ARDS and >6 units of FFP having a 72.7% higher risk of ARDS.[35] Other authors have shown this same relationship between the amount of FFP transfused and the development of ALI. In a retrospective study of critically ill medical patients, Khan et al. demonstrated that patients transfused with FFP had a higher likelihood of developing ALI (adjusted OR, 2.48; 95% CI, 1.29–4.74).[36] Further analysis by these authors showed a dose response of the number of units of FFP transfused to the development of ALI, with ≥4 units associated with a significantly increased risk for ALI. Our results echo many of the findings in the above-mentioned studies. Patients developing ALI received significantly more units of FFP that those who did not develop ALI (21.6 ± 14.6 vs. 11.7 ± 6.6; $p < 0.001$). Multivariate logistic regression also demonstrated an independent relationship between transfusion of FFP and the development of early ALI (adjusted OR, 1.2; 95% CI, 1.08–1.33; $p < 0.01$). However, our study does not include outcomes after FFP transfusion. As suggested above, FFP may have protective effects with lower mortality risks at the expense of the development of ALI. This increased risk of ALI/ARDS may be acceptable if higher ratios of FFP:PRBC transfusion prevents early death secondary to hemorrhage and coagulopathy.

This study is subject to several limitations. It is a prospective observational study of a specific group of trauma patients admitted to a CSH, which may not reflect civilian patient populations. All patients in this study were the victims of penetrating trauma, and 59% had wartime-type injuries from explosions often not seen in civilian trauma centers. As is the nature of many combat-related studies, several patients were excluded from our analysis because of missing data points; and it is unknown what effect these patients may have contributed to this study. Specific types of injuries were also not included in this study, as we only collected the mechanism of injury, presence of pulmonary injury, and presence of long bone fracture in this patient population. The average age of PRBCs given is unknown, and the amount of type-specific versus O-negative blood transfused in these patients. Most importantly, follow-up data were not available for analysis; hence, the relationship between the development of early ALI and outcomes could not be assessed.

The results of this study are concordant with previously published studies. The incidence of early ALI in our severely injured patient population was 33%. Patients who developed ALI were significantly more injured and required more blood products, including PRBC, FFP, and platelets, than those patients who did not develop ALI. Multivariate logistic regression showed that the presence of pulmonary injury had the greatest impact on the incidence of ALI, whereas the amount of FFP transfused was also independently associated with the development of ALI.

Does the potential benefit of a successful hemostatic resuscitation with FFP outweigh the risk of early ALI? This question can only be answered by randomized clinical trials

in severely injured trauma patients requiring large transfusions using these new resuscitation protocols.

REFERENCES

1. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma.* 2007; 62:307–310.
2. Borgman M, Spinella P, Perkins M, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma.* 2007;63:805–813.
3. Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma.* 2007;62:112–119.
4. Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. *Transfusion.* 2006;46:685–686.
5. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg.* 2008;248:447–458.
6. MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. *J Trauma.* 2006;60:S46–S50.
7. Spinella PC, Perkins JG, Grathwohl KW, et al. Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. *Crit Care Med.* 2007;35:2576–2581.
8. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma.* 2003;54:898–907.
9. Marik PE, Raghavan M. Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. *Chest.* 2005;127:295–307.
10. Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. *Transfus Med Rev.* 2004;18:184–188.
11. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA; TRALI Consensus Panel. Proceedings of a consensus conference: towards an understanding of TRALI. *Transfus Med Rev.* 2005;19: 2–31.
12. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European Consensus Conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. *Am J Respir Crit Care Med.* 1994;151:818–824.
13. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342:1301–1308.
14. Treggiari MM, Hudson LD, Martin DP, Weiss NS, Caldwell E, Rubenfeld G. Effect of acute lung injury and acute respiratory distress syndrome on outcome in critically ill trauma patients. *Crit Care Med.* 2004;32:327–331.
15. Poole GV, Ward EF, Griswold JA, Muakkassa FF, Hsu HS. Complications of pelvic fractures from blunt trauma. *Am Surg.* 1992;58:225–231.
16. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353:1685–1693.
17. Shah CV, Localio AR, Lanken PN, et al. The impact of development of acute lung injury on hospital mortality in critically injured trauma patients. *Crit Care Med.* 2008;36:2309–2315.
18. Holland MC, Mackersie RC, Morabito D, et al. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma.* 2003;55:106–111.
19. Hoyt DB, Simons RK, Winchell RJ, et al. A risk analysis of pulmonary complications following major trauma. *J Trauma.* 1993;35:524–531.
20. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks of development of the acute respiratory distress syndrome. *Am J Resp Crit Care Med.* 1995;151:293–301.
21. Miller PR, Croce MA, Kilgo PD, Scott J, Fabian TC. Acute respiratory distress syndrome in blunt trauma: identification of independent risk factors. *Am Surg.* 2002;68:845–850; discussion 850–851.
22. Cohn SM. Pulmonary contusion: review of the clinical entity. *J Trauma.* 1997;42:973–979.
23. Ljungman AG, Grum CM, Deeb GM, Bolling SF, Morganroth M. Inhibition of cyclooxygenase metabolite production attenuates ischemia-reperfusion lung injury. *Am J Rev Respir Dis.* 1991;143:610–617.
24. Batchinsky AI, Weiss WB, Jordan BS, Dick EJ Jr, Cancelada DA, Cancio L. Ventilation-perfusion relationships following experimental pulmonary contusion. *J Appl Physiol.* 2007;103:895–902.
25. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. *Am J Surg.* 1982; 144:124–130.
26. Miller PR, Croce MA, Bee TK, et al. ARDS after pulmonary contusion: accurate measurement of contusion volume identifies high-risk patients. *J Trauma.* 2001;51:223–228; discussion 229–230.
27. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005; 33:1191–1198.
28. Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis.* 1983;128:185–189.
29. Toy P, Popovsky MA, Abraham E, et al; National Heart, Lung and Blood Institute Working Group on TRALI. Transfusion-related acute lung injury: definition and review. *Crit Care Med.* 2005;33:721–726.
30. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. *Crit Care Med.* 2008;36:3080–3084.
31. Silliman CS. The two-event model of transfusion-related acute lung injury. *Crit Care Med.* 2006;34:S124–S131.
32. Croce MA, Tolley EA, Claridge JA, Fabian TC. Transfusions result in pulmonary morbidity and death after a moderate degree of injury. *J Trauma.* 2005;59:19–24.
33. Silverboard H, Aisiku I, Martin GS, Adams M, Rozycki G, Moss M. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. *J Trauma.* 2005;59: 717–723.
34. Sperry JL, Ochoa JB, Gunn SR, et al. An FFP:PRBC transfusion ratio ≥1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma.* 2008;65:986–993.
35. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma.* 2009;67:221–230.
36. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest.* 2007;131:1308–1314.

DISCUSSION

Dr. Andriy Batchinsky (US Army Institute of Surgical Research, Fort Sam Houston, TX): I enjoyed reading this well-written manuscript and would like to thank the program committee for the opportunity to serve as a reviewer.

Effects of combat damage control resuscitation on lung function are largely unknown. In this manuscript, Edens et al. demonstrated that casualties who received a higher (1:1) ratio of FFP:PRBC transfusions in the course of their treatment for traumatic injuries incurred a 33% incidence of ALI. Presence of pulmonary injury, initial tidal volume, higher volume of transfused FFP, and higher injury severity were associated with development of ALI. These findings are of high importance because the medical community largely under- appreciates the effects of transfusions and early post-trauma management as causes of deterioration in lung function which increase morbidity and mortality in trauma patients.

I have minor questions for the authors:

1. Clinical diagnosis of ARDS without chest X-rays is challenging. Did you review chest radiographs to solidify the clinical diagnosis of ARDS?
2. Based on what criteria was presence of pulmonary injury diagnosed or suspected?
3. Can you categorically state absence of blunt injuries when you had 59% of explosions as a mechanism of injury?

Some of those patients had to incur pulmonary contusion as a consequence of the blast component.

4. May I propose for your consideration that the causes of hypoxia in early hours after pulmonary contusion are development of true shunt and ventilation-perfusion mismatch. Coincidentally, this is the time when most resuscitation takes place. Failure to judiciously titrate fluid therapy in the early post-contusion time may result in flooding of partially ventilated alveoli and further increase in the amount of true shunt, which could contribute to development of ALI/ARDS.[1]

Thank you for the opportunity to review this manuscript and congratulations on your work.

REFERENCE

1. Batchinsky AI, Weiss WB, Jordan BS, et al. Ventilation-perfusion relationships following experimental pulmonary contusion. *J Appl Physiol*. 2007;103:895–902.

Dr. Jason W. Edens (US Army Institute of Surgical Research): Thank you, Dr. Batchinsky, for your critical review of this article and the insightful comments. We agree that the diagnosis of acute lung injury/acute respiratory distress syndrome is extremely difficult without chest radiographs, and on further review, it was verified that chest radiographs of all patients included in this study had been viewed by the deployed critical care staff on site (KKC, JCP). The appropriate changes have been made in the article. The presence of pulmonary injury was diagnosed in this patient population as any blunt or penetrating injury to the thorax that resulted in a contusion, hemothorax, or pneumothorax diagnosed clinically or with chest radiographs. Although patients were divided into categories with and without pulmonary injury, the exact pulmonary injury in each patient was not available in our database, and this is addressed in limitations section of the article.

In reference to your comment concerning our classification of the absence of blunt trauma in explosion injuries, we assume that, typical of many war injuries currently seen, patients suffering from explosions are not only injured by the blast but also from projectiles from the explosion itself. Although we admit that there is obviously a blunt component to explosions that can lead to pulmonary injuries such as contusion, hemothorax, or pneumothorax, many articles on war injuries have and are classifying explosion injuries as penetrating trauma, and we wished to continue this trend in our article.

We appreciate the reference provided for the article "Ventilation-perfusion relationships following experimental pulmonary contusion," which is a very insightful article to the physiology occurring during the initial resuscitation phase after pulmonary contusion. This article explains the interaction between fluid resuscitation and pulmonary contusion, and although most of the patients in our study required large volume, blood component resuscitations because of their medical conditions, it is clinically important to keep in mind the effects these resuscitations may have on patients.

Again, we wish to thank Dr. Batchinsky for his comments and review of our article.